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Involvement of macrophages in eosinophilic and non-eosinophilic chronic rhinosinusitis

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Abstract:

Purpose. This prospective immunohistochemical study aimed to evaluate the expression of tissue macrophages in eosinophilic (ECRS) and non-eosinophilic chronic rhinosinusitis (NECRS) and to correlate these findings with clinical and radiological disease severity in order to determine their clinical significance.

Methods. Disease severity was assessed by symptom questionnaires (VAS, SNOT-20), nasal endoscopy (Lund-Kennedy score), CT scan (Lund-Mackay score), allergy status, nasosinusal microbiology, and comorbid asthma or non-steroidal anti-inflammatory drug hypersensitivity. Mucosal tissue samples from 12 controls, 27 NECRS and 18 ECRS patients were stained for CD-68, a marker for macrophages, and macrophage-positive cells were counted in three hotspot high-power fields (×400) by two blinded observers.

Results. Immunohistochemical analysis showed that CD-68-positive macrophages were localized predominantly in the lamina propria of the sinonasal mucosa in all groups. There were no statistically significant differences in the number of tissue macrophages between the ECRS, NECRS and control groups. In the whole CRS group, CD-68 expression correlated positively with symptom duration ($r=0.402$; $p=0.006$), and a similar relationship was found within the ECRS group ($r=0.529$; $p=0.029$). A positive correlation between macrophage expression and clinical disease severity, assessed with the SNOT-20 questionnaire, was observed in both the ECRS and NECRS groups. Macrophage expression correlated with tissue eosinophilia only in the NECRS group.

Conclusion. Tissue macrophage infiltration does not differ quantitatively between eosinophilic and non-eosinophilic chronic rhinosinusitis or controls, suggesting that macrophage abundance alone does not distinguish these inflammatory endotypes. However, the correlation of macrophage expression with symptom duration and with SNOT-20-assessed disease burden in both phenotypes suggests that macrophages contribute functionally to disease chronicity and severity. Further studies incorporating M1/M2 macrophage phenotyping are warranted to clarify their mechanistic role in chronic rhinosinusitis.

1. Introduction

Chronic rhinosinusitis (CRS) is one of the most common otolaryngological conditions, affecting up to 11% of the European population [1]. Chronic inflammation causes tissue remodelling, which clinically manifests as nasal blockage, nasal discharge, facial pain and reduction of smell, and produces endoscopic signs such as nasal polyps, mucopurulent discharge, oedema, and corresponding mucosal changes on computed tomography [2]. The disease significantly impairs patients' quality of life [3] and is associated with substantial direct and indirect costs, mainly due to loss of productivity [4].

Patients with CRS develop a local inflammatory process in the tissue of the nasal mucosa and paranasal sinuses. CRS is currently divided into eosinophilic (ECRS) and non-eosinophilic (NECRS) subtypes, with ECRS characterised by tissue eosinophil infiltration, conventionally defined by a cut-off of 10 eosinophils per high-power field. ECRS and NECRS differ in the inflammatory patterns of the paranasal sinus mucosa: reaction types differ in the innate lymphoid cell subsets involved (ILC1, ILC2 or ILC3) as well as in the set of inflammatory cytokines secreted. Type 2 inflammation, characteristic of ECRS, is driven initially by the epithelial alarmins IL-25, IL-33 and thymic stromal lymphopoietin (TSLP), which in turn induce the downstream cytokines IL-4, IL-5 and IL-13; these alarmins are produced by several innate immune cell populations, including eosinophils, mast cells, macrophages, dendritic cells, basophils and neutrophils [5].

The distinct molecular pathways of eosinophilic and non-eosinophilic CRS are reflected clinically: eosinophilic CRS shows greater resistance to conventional pharmacological and surgical treatment and a higher recurrence rate. Consequently, efforts to implement biologic treatment (monoclonal antibodies) have focused predominantly on this patient group.

The role of innate immune cells, including macrophages, in the pathogenesis of CRS remains incompletely understood. Macrophages are innate immune cells with a central role in pathogen defence, antigen presentation and cytokine production, and can differentiate into pro-inflammatory classically activated (M1) or anti-inflammatory alternatively activated (M2) phenotypes depending on the local microenvironment. Determining the extent of macrophage infiltration in the microenvironment of the nasal and paranasal sinus mucosa may help clarify the pathogenesis of CRS and identify potential therapeutic targets.

The purpose of this prospective immunohistochemical study was to evaluate the expression of tissue macrophages in ECRS and NECRS and to correlate these findings with clinical and radiological disease severity in order to establish their clinical significance.

2. Materials and Methods

This prospective study was conducted at the Department of Otolaryngology, Centre of Postgraduate Medical Education (CMKP), Warsaw, Poland, between April 2019 and January 2022.

Fifty-seven adult patients qualified for surgery were enrolled. The study group consisted of patients qualified for first-time endoscopic sinus surgery (ESS) due to insufficient control of CRS after pharmacological treatment, in accordance with EPOS 2020 guidelines. The control group consisted of patients qualified for septoplasty because of impaired nasal patency caused by nasal septal deviation, with no clinical, endoscopic or radiological signs of CRS.

All study-group patients underwent a standardised clinical assessment including symptom severity rated on a visual analogue scale (VAS, 0–10) and the 20-item Sino-Nasal Outcome Test (SNOT-20) questionnaire, assessment of comorbidities (asthma, diagnosed by spirometry according to GINA recommendations; allergy, diagnosed by skin prick testing), endoscopic examination scored with the Lund-Kennedy score, CT scan of the sinuses scored with the Lund-Mackay score, routine laboratory tests, including a peripheral complete blood count with differential (leukocytes, neutrophils, lymphocytes, monocytes, basophils and eosinophils, expressed as absolute counts and percentages) and coagulation parameters (INR, prothrombin time, activated partial thromboplastin time), and a nasal swab for bacterial

and fungal culture. Patients were classified as eosinophilic CRS (ECRS) when the mean tissue eosinophil count was ≥10 per high-power field (×400) and as non-eosinophilic CRS (NECRS) when it was <10 per high-power field.

Exclusion criteria were a diagnosis of oncological disease, cystic fibrosis, primary ciliary dyskinesia, systemic vasculitis, fungal sinusitis, antrochoanal polyps, gastroesophageal reflux disease, prior ESS, immunotherapy, antibiotic treatment within the 12 weeks preceding surgery, and use of oral or other known immune-modulating drugs.

A section of mucosa was obtained from the uncinate process area of all patients during surgery under general anaesthesia. Tissue was fixed in 10% formalin, embedded in paraffin, and cut into 4-µm sections, stained as previously described with slight modifications [6]. After standard deparaffinisation in xylene and rehydration through a graded ethanol series (100%, 96%, 70%), heat-induced antigen retrieval was performed at pH 9.0 in a bath pre-heated to 98°C for 30 minutes. Following Peroxidase Block and Protein Blocker steps, sections were immunostained with a primary anti-CD68 antibody (1:100, ab201973, Abcam), incubated for one hour, followed by a post-primary antibody for 30 minutes, according to the manufacturer's instructions for the NovoLink Polymer Detection System. Sections were then counterstained with haematoxylin, dehydrated, and coverslipped. Positive cells were counted in three hotspot fields at ×400 magnification by two authors blinded to the clinical data, using light microscopy. Standard haematoxylin and eosin staining was also performed in all patients to determine tissue eosinophilia.

Statistical analysis was performed using the R programming language (v4.2.2) in RStudio (v2023.03.0). The level of statistical significance was set at $p<0.05$.

The study was approved by the Local Ethics Committee of the Centre of Postgraduate Medical Education, Warsaw (approval no. 50/PB/2019). All patients gave their written consent to take part in the study.

3. Results

Fifty-seven patients were included in the study; their baseline demographic and clinical characteristics are provided in Table 1.

Table 1. Preoperative demographic and clinical characteristics of study participants

Characteristic	Control (n=12)	NECRS (n=27)	ECRS (n=18)
Age (years), median (range)	35 (19–60)	47 (19–71)	48.5 (26–69)
Gender (F/M)	3/9	9/18	9/9
CRS with nasal polyps, n (%)	0	7 (25.9)	14 (77.8)
Allergy, n (%)	1 (8.3)	7 (25.9)	10 (55.6)
Asthma, n (%)	0	1 (3.7)	4 (22.2)
NSAID hypersensitivity, n (%)	0	0	2 (11.1)
Nasal polyp grade, median (range)	0 (0–0)	0 (0–4)	4.5 (0–8)
Endoscopic score (LKS), mean (range)	1.1 (0–4)	4 (0–7)	7.5 (3–11)
CT score (LMS), mean (range)	0.2 (0–2)	9 (5–21)	15.5 (6–24)
Positive bacterial culture, n (%)	1 (8.3)	4 (14.8)	5 (27.8)
Nasal obstruction (VAS), median (range)	7 (2–10)	8 (2–10)	8.5 (4–10)
Rhinorrhoea (VAS), median (range)	7.5 (0–10)	7 (0–10)	8 (5–10)
Facial pain (VAS), median (range)	4.5 (0–10)	2 (0–10)	3.5 (0–8)
Olfactory impairment (VAS), median (range)	2.5 (0–8)	2 (0–10)	6 (0–10)
SNOT-20 total score, median (range)	27.5 (1–68)	33 (7–78)	38 (13–78)
Tissue eosinophils (no./hpf, ×400), mean (SD)	NA	0.815 (1.66)	90.9 (69.9)

NA, not applicable; VAS, visual analogue scale; SNOT-20, 20-item Sino-Nasal Outcome Test; LKS, Lund-Kennedy score; LMS, Lund-Mackay score. LKS and LMS are presented as mean (range); tissue eosinophil counts are presented as mean (SD); all other continuous variables are presented as median (range).

3.1. Baseline clinical severity

CRS patients were significantly older than controls, and ECRS patients were significantly older than NECRS patients. Olfactory impairment was significantly more pronounced in ECRS than in NECRS patients. Endoscopic findings, including total Lund-Kennedy score and the oedema and nasal polyp sub-scores, were significantly greater in ECRS than in NECRS patients. Radiological severity, assessed by the Lund-Mackay score, was significantly highest in the ECRS group, intermediate in the NECRS group, and lowest in controls. The percentage and absolute number of peripheral blood eosinophils differed significantly between the ECRS, NECRS and control groups. Tissue eosinophil counts also differed significantly overall between the three groups, driven by significantly higher values in ECRS than in both NECRS and controls, whereas NECRS and control values did not differ significantly from each other.

3.2. Tissue macrophage (CD-68) expression

Immunohistochemical staining showed that CD-68-positive macrophages were localised predominantly in the lamina propria of the sinonasal mucosa. The distribution of infiltrating CD-68-positive cells in controls, NECRS and ECRS patients is shown in Figure 1.

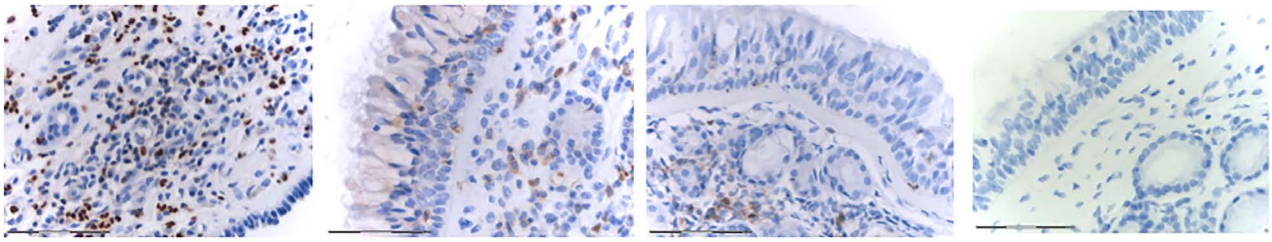


Fig. 1. *Representative immunohistochemical staining for CD-68 in the sinonasal mucosa of control, NECRS and ECRS patients (×400), with an isotype negative control. Scale bar 100 µm.*

There were no statistically significant differences between the study groups in the number of CD-68-positive tissue macrophages (Fig. 2).

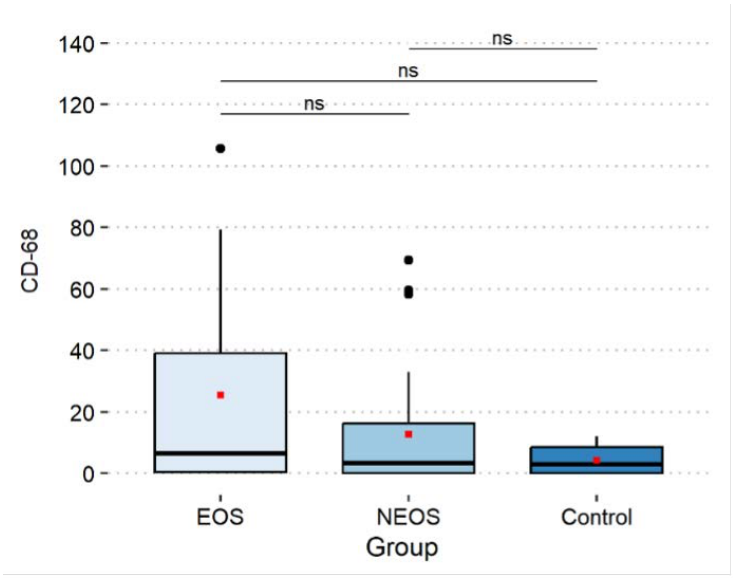


Fig. 2. *Number of CD-68-positive macrophages in mucosal specimens of the control, NECRS ("NEOS") and ECRS ("EOS") groups. Box-and-whisker plots represent the median, lower and upper quartile, and minimum and maximum values; dots indicate outliers; ns, not significant.*

3.3. Correlations between macrophage expression and clinical parameters

In the whole group of CRS patients, CD-68 expression correlated positively with symptom duration (r=0.402; p=0.006); a similar relationship was observed within the ECRS subgroup (r=0.529; p=0.029). A positive correlation was found between macrophage expression and clinical disease severity, as assessed by the SNOT-20 questionnaire, in both the ECRS and NECRS groups. Macrophage expression also correlated significantly with tissue eosinophil count, but only within the NECRS group. Additional correlations between CD-68 expression and clinical, endoscopic and laboratory parameters in each study group are presented in Figure 3.

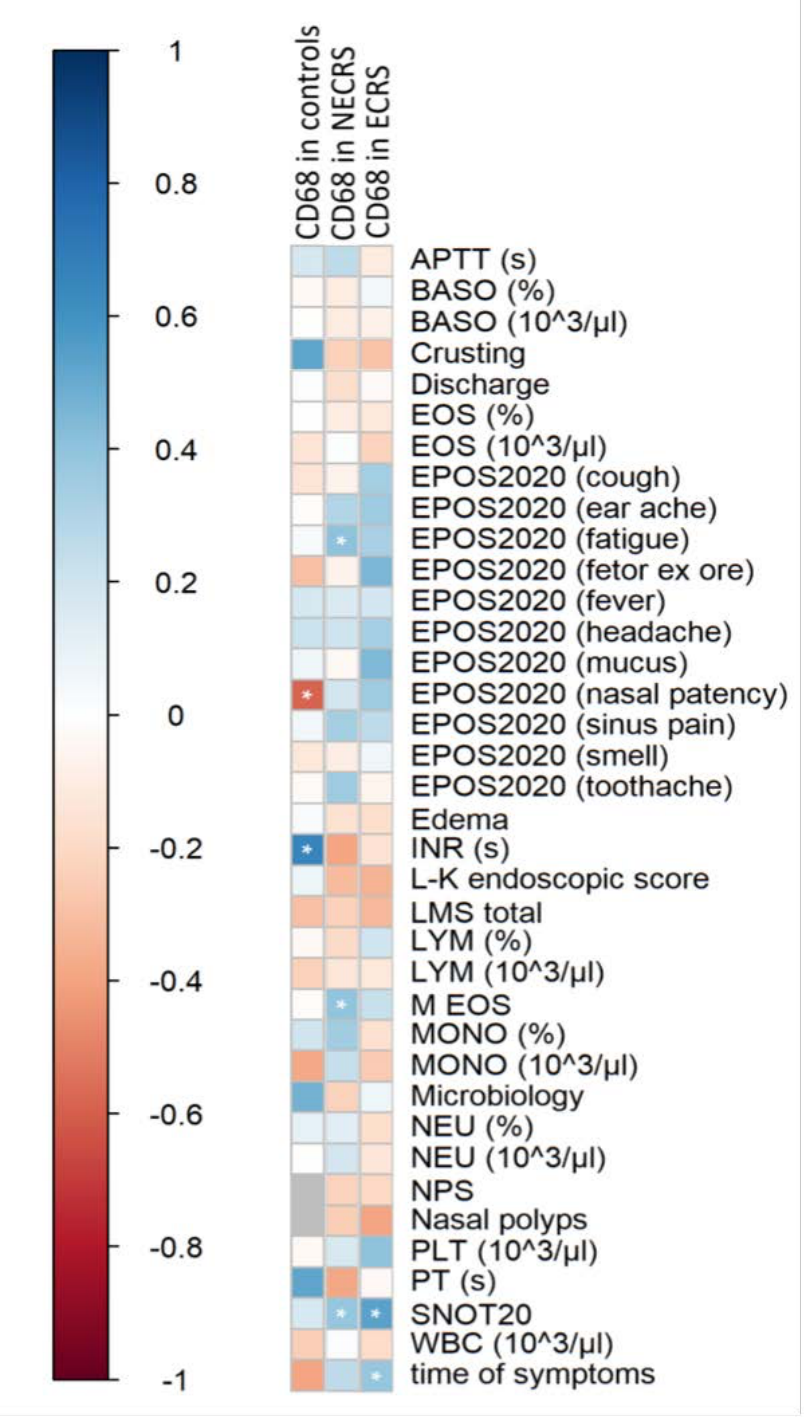


Fig. 3. *Correlation matrix between CD-68-positive cell expression and clinical, endoscopic, radiological and laboratory variables in the control, NECRS and ECRS groups. Asterisks indicate statistically significant correlations (p<0.05); M EOS – mean tissue (mucosal) eosinophil count; NPS: Nasal Polyp Score.*

4. Discussion

Macrophages are innate immune cells that play a central role in pathogen defence, antigen presentation and cytokine production. Classically activated (M1) macrophages are induced by IFN- , TNF- or bacterial products such as lipopolysaccharide and release the pro-inflammatory cytokines IL-12, IL-1 and TNF- , driving a type 1 response. Alternatively activated (M2) macrophages are induced by the type 2 cytokines IL-4 and IL-13 and release growth factors (TGF- 1, VEGF, PDGF) and the anti-inflammatory cytokine IL-10 [7]. Macrophages are similarly implicated in other airway inflammatory diseases, including asthma and chronic obstructive pulmonary disease, in which they have been associated with resistance to corticosteroid treatment [8-10].

In our study we performed a qualitative and quantitative assessment of CD-68-positive cells in the lamina propria of the nasal mucosa and correlated these findings with clinical, endoscopic, radiological and laboratory parameters.

Previous studies examining macrophage abundance in CRS have produced heterogeneous results. Several reports found increased numbers of CD-68-positive macrophages in CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) compared with controls [8,11-13,15], although the difference was not always statistically significant [18]. Tissue macrophage counts have also been reported to be higher in ECRS than in NECRS in some series [11-13], while other studies found no such difference [14-16]. Some authors have reported that CRSwNP tissue, irrespective of atopic status, contains more macrophages than CRSsNP tissue [5,8,15,19], while others found no significant difference between these groups [14,20]. Macrophage mannose receptor, which is important for antigen recognition and pathogen-macrophage interaction, is up-regulated in CRSwNP compared with CRSsNP or controls [21]. Notably, the site of tissue sampling appears to influence macrophage counts: uncinate process tissue from CRSwNP patients has been reported to contain more CD-68-positive cells than nasal polyp tissue from the same patients [5].

With regard to macrophage polarisation, M2 macrophages have been found to be more abundant in CRSwNP than in CRSsNP [22,23] and controls [24], correlating positively with IL-5, eosinophil cationic protein and locally produced IgE, and negatively with IL-6, IL-1 and IFN- ; this M2 predominance has also been linked to impaired phagocytosis of Staphylococcus aureus in CRSwNP [22]. In a Chinese cohort, both M1 and M2 macrophage numbers were increased in eosinophilic and non-eosinophilic CRSwNP compared with control tissue, but eosinophilic CRSwNP was characterised by fewer M1 and more M2 macrophages, resulting in a lower M1/M2 ratio than in non-eosinophilic CRSwNP [25]; conversely, another study found no difference in M1 cell numbers between CRSwNP and CRSsNP [23]. Among patients with eosinophilic CRSwNP, the number of IL-10-producing M2 macrophages correlated negatively with total symptom scores, polyp size, CT score and overall inflammatory cell counts, suggesting that a deficiency of IL-10 production by M2 macrophages may sustain chronic inflammation in this phenotype [25].

A bidirectional relationship between macrophages and eosinophils has also been proposed: eosinophils may release chemokines that recruit macrophages [13], while macrophages in the nasal mucosa are themselves a source of eotaxin, contributing to eosinophil recruitment [8]. In nasal polyp tissue, macrophages have been identified as the predominant cellular source of IL-17A, implicated in the pathogenesis of CRSwNP and proposed as a potential therapeutic target [17], and as the main cell type positive for phosphorylated MLKL, a marker of necroptotic cell death [26]. M2 macrophages further contribute to tissue remodelling in CRSwNP through overproduction of coagulation factor XIII-A and excessive submucosal fibrin deposition [27], have been associated with eosinophilic infiltration in nasal polyps [22,28], play a role in allergic asthma [29], and are a major cellular source of CCL18, a chemokine involved in lymphocyte and dendritic cell recruitment, fibroblast activation and maintenance of local inflammation in CRSwNP [30].

In our cohort, macrophages were found predominantly in the lamina propria of the mucosa, consistent with previous reports [25]. We did not find statistically significant differences in the number of CD-68-positive cells

between ECRS, NECRS and control groups, despite the clear gradient of clinical, endoscopic and radiological severity across these groups. This suggests that macrophage abundance, in absolute terms, does not distinguish CRS endotypes as clearly as it does for tissue eosinophilia. However, CD-68 expression correlated with symptom duration in the whole CRS group and, more strongly, in the ECRS subgroup, and with SNOT-20-assessed disease burden in both ECRS and NECRS, indicating that macrophages may nonetheless contribute functionally to symptom chronicity and severity independent of their absolute numbers. The correlation between macrophage expression and tissue eosinophilia observed only in the NECRS group is consistent with reports that immune-cell cross-talk, including between macrophages and eosinophils, differs qualitatively between eosinophilic and non-eosinophilic CRS phenotypes [32].

4.1. Strengths and limitations

The main strength of this study is its prospective data collection design. Several limitations should be acknowledged. We did not assess macrophage polarisation (M1 vs M2 phenotype), which may be more informative than absolute macrophage count for distinguishing CRS endotypes and merits investigation in future studies, together with the potential immunoregulatory role of M2 macrophages in CRS. The relatively small size of the study groups, particularly the control and ECRS groups, limits statistical power, and larger cohorts are needed to confirm these findings. The control group consisted of patients with nasal septal deviation; although these patients had no clinical, endoscopic or radiological evidence of CRS, septal deviation has been associated with squamous cell metaplasia and lymphocytic infiltration of the nasal mucosa [31], and its potential influence on the immunohistochemical findings cannot be fully excluded. Finally, atopy was defined on the basis of systemic measures (skin prick testing) rather than local markers; local IgE production may be elevated in some CRSwNP patients in the absence of systemic atopy, which could not be captured by our study design.

5. Conclusions

Tissue CD-68-positive macrophage infiltration in the lamina propria of the sinonasal mucosa does not differ significantly in absolute number between eosinophilic CRS, non-eosinophilic CRS and controls, despite a clear gradient of clinical, endoscopic and radiological disease severity across these groups. Macrophage expression correlates with symptom duration and with SNOT-20-assessed disease burden in both CRS phenotypes, and with tissue eosinophilia in non-eosinophilic CRS, suggesting that macrophages contribute functionally to disease chronicity and severity rather than serving as a simple quantitative marker distinguishing CRS endotypes. Further studies incorporating M1/M2 macrophage phenotyping in larger cohorts are warranted to clarify the mechanistic role of macrophages in chronic rhinosinusitis and their potential as a therapeutic target.

Supplementary Materials: Not applicable.

Acknowledgments: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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